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Description

BACKGROUND OF THE INVENTION

I. Field of the Invention

The present invention is directed generally to the iontophoretic transport of ions for therapeutic purposes. More particularly, it involves the use of a direct current stimulus to transport cardioactive drugs such as antiarrhythmia, vasodilators, inotropic drugs to cardiac tissue.

II. Discussion of the Related Art

Implantable defibrillator devices have been under development and use for some time. This device is used for the correction of either ventricular tachycardia (abnormally rapid heart rate) or ventricular fibrillation (an extremely rapid heart beat disorder) by discharging electrical energy into the heart normally between internally placed electrodes. The electrode arrangement may include two large patches which are placed on the epicardial or pericardial surface adjacent the heart tissue. When the implantable defibrillator senses or recognizes ventricular tachycardia or fibrillation the implantable defibrillator discharges, normally with about 30 joules of electrical energy via the two patches. The current utilized for the devices is supplied by a battery powered pulse generator implanted under the skin of the patient.

Ventricular arrhythmias in patients with coronary heart disease and myocardial infarction probably originate from the areas of slow conduction within the previously infarcted myocardium region. Most patients with sustained monomorphic ventricular tachycardia have various degrees of myocardial scar secondary to obstructed coronary arteries.

The efficacy of antiarrhythmic medication is related to concentration of the drug at the arrhythmogenic area. Since most antiarrhythmic drugs require high myocardial tissue concentrates to be effective, high dose intake of such drugs will lead to high plasma concentrations and with it high incidence of toxic side effects.

Iontophoretic transport of ions is a technique in which positive or negative ions are driven into tissue of interest by current applied between two electrodes one of which contains a supply of the material to be transported. Iontophoresis for therapeutic purposes by means of a direct current was introduced in 1908 by Leduc. Since then it has been introduced in several fields such as transdermal delivery of steroids to joints, as well as transdermal delivery of local anesthetics, facilitated transdermal transport of insulin, and the like.

US-A- 4 639 244 discloses an implantable electrophoretic pump for ionic drugs, which uses the principle of iontophoresis.

A system which provides for the subcutaneous injection of a drug into an implanted reservoir connected to the heart by a pacer lead is described in U.S.-A- 4,774,951 to Osypka. Other references teach the delivery of drugs to a treatment site through techniques and methods such as porous electrode leads, by dissolving slowly from an immobilized site, or by osmosis through a permeable membrane.

The present invention relates to an iontophoretic drug delivery apparatus as is set out in claim 1, whose pre-characterising part is based on US-A- 4 774 951, and the distinguishing features of the present invention are set out in the characterising part of claim 1.

By means of the present invention, appropriate drugs can be transported at high concentration to the site of interest where time and concentration are of the essence. The delivery apparatus maximizes the concentration of the drug in the site of interest and minimizes the systemic concentration of the medication, thereby reducing side effects.

The apparatus generally consists of a pair of electrodes, including anodic and cathodic electrodes, one of which is designed to dispense the medication of interest, proximately located with respect to the tissue of interest and connected by electrical leads to a subcutaneous independent source of electricity. A subcutaneously situated pouch is provided for containing the drugs of interest. The implanted pouch is designed to be subcutaneously replenished through the skin with a relevant drug from time to time. The pouch is connected with the administering electrode of the electrode system via a pumping mechanism connected by a tube from the storage compartment to the proper patch electrode.

In the illustrated embodiment, the medication is an antiarrhythmic drug which may utilize an existing implantable defibrillator device as a power source or it may be connected to a specially designed power source. The implantable defibrillator unit is embedded over the abdomen under the skin and the antiarrhythmic storage compartment is designed to be replenished subcutaneously by connection inlet. The electrical system installed in connection with the automatic implantable cardioverter defibrillator provides the means by which appropriate antiarrhythmic medication is transported and iontophoretically delivered with maximum concentration to the arrhythmogenic site. The pumping mechanism is configured to be powered from the implantable defibrillator power source. The implantable pump would be similar to the implantable pumps used primarily for chemotherapy and insulin

drug delivery. These include a bellows-type pump manufactured by Infusid Corporation of Sharon, MA which can be subcutaneously refilled with a drug. That pump is fluorocarbon charged and the pressure created by the fluorocarbon vapors provides the power for the pump which operates at about 300 mm of mercury greater than atmospheric pressure.

For antiarrhythmia control, the iontophoretic drug delivery apparatus recognizes the arrhythmia and its programmable computerized control system triggers the pumping mechanism in response to runs of ventricular tachycardia. The pump delivers the antiarrhythmic medicine from the storage compartment to the anodal pole of the patch system which is installed over the arrhythmogenic area. Current pulses to the patch electrode accomplish iontophoretic delivery of the drug.

A small amount, such as one milliamp/cm^2 or less, of current can be delivered through the anodal patch in approximately 100 msec pulses synchronized with the ventricular depolarization. The iontophoretic current should be delivered during ventricular refractory periods so as to avoid any ventricular depolarization by the iontophoretic system. The drug delivery into the myocardium may occur in response to runs of ventricular tachycardia in an attempt to chemically interrupt the arrhythmia or at fixed intervals to maintain constant tissue levels of the drug. In addition, the medicine can be delivered with implantable defibrillator discharge which will provide the electromotive force which will transport the drug iontophoretically into the myocardium.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings wherein like numerals are utilized to designate like parts throughout the same:

Figure 1 is a schematic representation of the iontophoresis apparatus of the invention;

Figure 2 is a top view of the drug delivering patch electrode

Figure 3 is a side elevational view of the patch electrode of Figure 2; and

Figure 4 is a schematic block diagram of the apparatus of the invention.

DETAILED DESCRIPTION

The present invention relates to iontophoretic delivery of drugs to internal tissue and is illustrated by the application of such a system to an implantable defibrillator. The electrical system of the implantable defibrillator provides the electrical current by which appropriate antiarrhythmic medication can be transported; but, of course, the application of the invention is not intended in any manner to be restricted to use only in conjunction with an implantable defibrillator. The delivery apparatus maximizes concentration drug in the arrhythmic site and minimizes the overall or systemic concentration of the medication, thereby reducing side effects. Since the implantable defibrillator is capable of recognizing ventricular tachycardia or fibrillation, its computerized control system is utilized to trigger a pumping mechanism in response to runs of ventricular tachycardia or at fixed intervals to maintain high drug concentrations in the tissues. Iontophoretic current is controlled to be delivered during ventricular refractory periods to avoid any ventricular depolarization problems.

The pump then can deliver the arrhythmic medication, or any charged cardioactive medication, from a storage compartment to the anodal pole of the patch system which has previously been placed over the arrhythmogenic area of the heart. An example of such system incorporated into the implantable defibrillator will now be described in greater detail with reference to the accompanying drawings.

As shown in Figure 1, the apparatus is installed with reference to the heart of a patient shown generally at 10. It includes a rather large anodal patch electrode 11 which is normally designed to be installed over and addressing a previous infarct or known arrhythmogenic region of the heart. This patch electrode is best depicted in Figures 2 and 3. A second patch electrode facing the anterior patch is provided at 12. The anodal electrode 11 has a drug inlet port 13 which is connected to a drug reservoir outlet port 14 via a tube 15 and is also provided with a drug outlet port 16 connected to a discharge tube as at 17.

The electrode 11 also has a conductor grid area 18 in the form of metallic mesh. A similar conductor grid is provided with respect to the cathode 12 as at 19. As can better be seen in Figure 3, the mesh 18 of the electrode 11 is further covered by an outer silicone lining 20 which overlays the entire system and protects it from the surrounding tissues and body fluids. A similar lining surrounds the system of the electrode 12 similarly protecting it from the surrounding tissues and bodily fluids. The mesh 18 is exposed to the inner chamber 21 of the electrode 11 which, in one embodiment, had a nominal thickness of 4 mm. Chamber 21 interfaces with the epicardial surface to which the patch electrode 11 is attached via permeable membrane 22.

The apparatus is further provided with a chamber 23 which includes a subcutaneous resupply port 24 and contains the batteries or source of electrical current (not shown) for the implantable defibrillator and iontophoresis apparatuses together with the drug pump, also not shown.

Bipolar electrogram electrodes 25 and 26 are attached to the heart via devices 27 and 28 (Figure 1), respectively, which are attached to input leads 29 and 30 in a well-known manner. These electrodes provide input data with respect to the operation of a heart and act to control the implantable defibrillator and iontophoresis apparatuses. Implantable defibrillator electrical leads 31 and 32 are also provided connecting the source of implantable defibrillator electrical energy with the anodic and cathodic patch electrodes, respectively. Since the implantable defibrillator unit is embedded over the abdomen under the skin, the antiarrhythmic storage compartment included in the chamber 23 can be designed to be easily replenished subcutaneously, as via port 24.

Figure 4 is a schematic block diagram of the apparatus of the invention including a pump (34), power source or battery (35), and control device (36) which controls both the power source and pump in relation to inputs from the bipolar electrogram recorded by the sensing electrodes indicating the rhythm state of the heart. As seen in the schematic of Figure 4, the implantable defibrillator will incorporate the drug chamber and the pump will be powered from the implantable defibrillator power source 35, as determined by the control device 36 which may be microprocessor operated in a well-known manner.

With respect to the pump, currently there are several proven implantable pump systems primarily designed for chemotherapy and insulin drug delivery. One such pump is made by Infusid Corporation of Sharon, MA which is fluorocarbon-charge bellows-type pump which can be subcutaneously refilled with a drug. The pressure created by the fluorocarbon vapors provides the power for this pump and it operates at about 300 mm of mercury above atmospheric pressure. In addition, other pumps are under development including peristaltic-type insulin pumps for implant use which are expected to be available shortly.

Given the state-of-the-art of implantable pumps, incorporation into the iontophoretic drug delivery apparatus within the implantable defibrillator unit is indeed feasible. However, it must be remembered that unlike the long term administration applications for which the pumps have been previously used, the drug delivered in the apparatus of the invention would be transported to the heart tissue quickly as indicated by the condition of the heart or at fixed intervals to maintain constant drug levels within the tissues. Any excess of the drug delivered by the pump to the patch electrode 11 must either be returned to the storage chamber or discarded. It may be secreted into the pericardial or the chest cavity as by tube 17 from which it can be passively absorbed into the systemic circulation of the patient. Even when secreted or vented in this manner, the amount of drug absorbed in the system of the patient will produce systemic concentrations far less than that required to produce any side effects in the patient.

In operation, the implantable defibrillator through the electrodes 25 and 26 recognizes ventricular tachycardia or fibrillation, following this when defibrillation is indicated the implantable defibrillator discharges with approximately 30 joules via the two large patch electrodes 11 and 12 placed on the heart surfaces. In conjunction with this, or in certain instances instead of the delivery of a defibrillating discharge, the system will activate the pump 34 to deliver an amount of drug from the storage area to the anodic or positive patch electrode 11. Simultaneously, a small amount of current such as 1 mA/cm^2 adjusted to an amount below the capture threshold is delivered through the anodal patch in approximately 80-100 msec pulses synchronized with the ventricular depolarization. This iontophoretic current is delivered during ventricular refractory so as to avoid any ventricular depolarization by the iontophoretic apparatus. The drug delivery into the myocardium may occur at fixed intervals to sustain constant tissue concentration or in response to runs of ventricular tachycardia as recognized by the electrodes 25 and 26 and in an attempt to chemically interrupt the arrhythmia. It can be delivered with the implantable defibrillator discharge so as to prevent recurrence of tachyrhythmias and the necessity of multiple discharges by the implantable defibrillator.

Preliminary studies performed on dogs have indicated that the delivery of antiarrhythmic drugs such as procainamide can be done quite successfully. Procainamide is a highly charged and small molecule; and, thus, is are especially well suited for iontophoretic delivery.

Animal studies have been performed during the last 18 months. Procainamide drug concentration was evaluated in the coronary sinus as well as in systemic circulation. In addition, drug concentration was evaluated transmyocardially using HPLC techniques in areas of chronically infarcted myocardium and in non-infarcted myocardium, areas which were not exposed to iontophoretic transport. Procainamide concentration in the myocardial tissues was 100 times of what is expected to be delivered using IV route. The concentration was much higher in the epicardial surface than in the endocardial surface. However, even within the endocardial surface, drug concentration was sufficient to render sustained monomorphic ventricular tachycardia noninducible for over three hours. On the other hand, tissues remote from the site of iontophoretic transport had very low concentration of procainamide detected and no electrical changes were

noted in them.

Given these preliminary results use of the invention is extremely encouraging with respect to the efficacy of the iontophoretic drug transport. It is believed that a great deal better control of life threatening arrhythmic conditions can be achieved by means of the drug delivery system of the invention.

Claims

1. An implantable delivery apparatus for use in applying medicinal materials rapidly to specific tissue sites of interest, the apparatus comprising first and second electrodes (11,12) proximately positionable with respect to the tissue site of interest and connected by leads (31,32) to a source (35) of electricity, wherein said first electrode (11) is further adapted to receive, contain and dispense medication from a stored supply thereof into proximate tissue of interest; storage means (23) for storing a supply of said medication and connected via conduit means (15) with said first electrode (11); pulse generating means for generating a series of electric current pulses; circuit means (31,32) connected to said source for supplying current pulses to said electrodes (11,12); characterised by pump means (34) for supplying an amount of said medication from said storage means (23) to said first electrode means (11) on demand; condition sensing means (25,26) for sensing medical conditions in the tissue of interest requiring application of said medication to the tissue of interest; and computerized control means (36) for activating and deactivating said pump means (34) and said pulse generating means in response to sensed conditions or in fixed interval form, wherein the circuit means (31,32) supplies a series of benign electric pulses to the first electrode in response to said sensed conditions and said second electrode is disposed to cooperate with said first electrode to cause iontophoretic infusion of the medicinal material in the desired direction to supply the medication into the proximate tissue of interest.

2. The apparatus of Claim 1 wherein said tissue of interest for example is an arrhythmogenic site of infarcted heart tissue, said electrodes (11, 12) are defibrillator patch electrodes and said electrodes and said medicine is an antiarrhythmic drug.

3. The apparatus of Claim 1 or 2 wherein said first electrode (11) further comprises an inlet (13) or receiving medication from said storage means (23), a storage chamber (21) separated from said tissue by a permeable membrane (22) through which said medicine can be infused and a discharge port (16) through which unused medicine can be secreted.

4. The apparatus of any preceding claim, wherein the storage means (23) is a subcutaneously implantable pouch.

5. The implantable apparatus of any preceding claim in conjunction with an implantable defibrillator, wherein said source (35) is

a source of electricity for the implantable defibrillator,

the circuit means (31, 32) being connected to said source (35) for supplying defibrillating current pulses to said electrodes (11, 12);

the condition sensing means (25, 26) being operable to serve medical conditions in said tissue of interest requiring defibrillation; and said

control means (36) being operable to activate and deactivate said defibrillation pulsing in response to sensed conditions or in fixed interval form.

Patentansprüche

1. Implantierbare Abgabevorrichtung für die schnelle Abgabe von medizinischem Material an interessierende spezifische Gewebestellen, wobei die Vorrichtung umfaßt: eine erste und zweite Elektrode (11, 12), die in der Nähe bezüglich der interessierenden Gewebestelle anordenbar und mittels Leitungen (31, 32) mit einer Elektrizitätsquelle (35) verbunden sind, wobei die erste Elektrode (11) ferner angepaßt ist, Medikation von einer gespeicherten Versorgung aufzunehmen, zu enthalten und in das nächstgelegene interessierende Gewebe zu verteilen; eine Aufbewahrungseinrichtung (23) zum Speichern einer Versorgung der Medikation, die mittels einer Leitungseinrichtung (15) mit der ersten Elektrode (11) verbunden ist; einer Impulsgeneratoreinrichtung zum Erzeugen einer Reihe von elektrischen Stromimpulsen; eine Schaltungseinrichtung (31, 32), die mit der Quelle verbunden ist, um Stromimpulse zu den Elektroden (11, 12) zu liefern; **gekennzeichnet durch** eine Pumpeinrichtung (34), um bei Bedarf eine Menge der Medikation von der Aufbewahrungseinrichtung (23) zur ersten Elektrodeneinrichtung (11) zu liefern; eine Zustandserfassungseinrichtung (25, 26) zum Erfassen medizinischer Zustände in dem interessierenden Gewebe, die das Aufbringen der Medikation auf dem interessierenden Ge-

webe erfordern; und eine computerisierte Steuereinrichtung (36) zum Aktivieren und Deaktivieren der Pumpeinrichtung (34) und der Impulserzeugungseinrichtung in Reaktion auf die erfaßten Bedingungen oder in einer feststehenden Intervallform, wobei die Schaltungseinrichtung (31, 32) eine Reihe von günstigen elektrischen Impulsen zur ersten Elektrode in Reaktion auf die erfaßten Bedingungen liefert, und wobei die zweite Elektrode derart angeordnet ist, daß sie mit der ersten Elektrode zusammenwirkt, um eine iontophoretische Infusion des medizinischen Materials in der gewünschten Richtung zu bewirken, um die Medikation in das nächstliegende interessierende Gewebe zu liefern.

2. Vorrichtung nach Anspruch 1, bei welcher das interessierende Gewebe beispielsweise eine arrhythmogenische Stelle eines infarktierten Herzgewebes ist, wobei die Elektroden (11, 12) Defibrillatorfleckenelektroden sind und das Arzneimittel ein antiarrhythmisches Arzneimittel ist.

3. Vorrichtung nach Anspruch 1 oder 2, bei welcher die erste Elektrode (11) weiterhin einen Einlaß (13) zur Aufnahme der Medikation von der ersten Aufbewahrungseinrichtung (23) aufweist, eine Aufbewahrungskammer (21), die vom Gewebe durch eine durchlässige Membran (22) getrennt ist, durch welche das Arzneimittel eingeleitet werden kann, und eine Abgabeöffnung (16), durch die nicht verwendetes Arzneimittel abgeschieden werden kann.

4. Vorrichtung nach einem der vorhergehenden Ansprüche, bei welcher die Aufbewahrungseinrichtung (23) ein subkutan implantierbarer Beutel ist.

5. Implantierbare Vorrichtung nach einem der vorhergehenden Ansprüche in Verbindung mit einem implantierbaren Defibrillator, wobei die Quelle (35) eine Elektrizitätsquelle für den implantierbaren Defibrillator ist, wobei die Schaltungseinrichtung (31, 32) mit der Quelle (35) zum Liefern von defibrillierenden Stromimpulsen zu den Elektroden (11, 12) verbunden ist;
wobei die Zustandserfassungseinrichtung (25, 26) derart betreibbar ist, daß sie die medizinischen Zustände im interessierenden Gewebe erfaßt, das die Defibrillation erfordert; und wobei
die Steuereinrichtung (36) derart betätigbar ist, daß sie das Defibrillationspulsieren in Reaktion auf die erfaßten Bedingungen oder in einer feststehenden Intervallform aktiviert und deaktiviert.

Revendications

1. Appareil implantable de distribution destiné à être utilisé pour appliquer rapidement des substances médicinales à des sites tissulaires d'intérêt spécifiques, l'appareil comprenant des première et seconde électrodes (11,12) pouvant être positionnées à proximité du site tissulaire d'intérêt et connectées par des fils (31,32) à une source (35) d'électricité, dans lequel ladite première électrode (11) est aussi adaptée pour recevoir, contenir et délivrer une médication depuis une source stockée de cette médication dans le tissu d'intérêt proche ; un moyen de stockage (23) destiné à stocker une source de ladite médication et connecté par l'intermédiaire d'un moyen de conduit (15) à ladite première électrode (11); un moyen générateur d'impulsions destiné à générer une série d'impulsions de courant électrique ; un moyen de circuit (31,32) connecté à ladite source pour fournir des impulsions de courant auxdites électrodes (11,12) ; caractérisé par un moyen de pompe (34) destiné à fournir une quantité de ladite médication depuis ledit moyen de stockage (23) jusqu'audit premier moyen d'électrode (11), à la demande ; des moyens de détection d'états (25,26) destinés à détecter des états médicaux dans le tissu d'intérêt nécessitant l'application de ladite médication au tissu d'intérêt ; et un moyen de commande informatisé (36) destiné à activer et à désactiver ledit moyen de pompe (34) et ledit moyen générateur d'impulsions en réponse aux états détectés ou à des intervalles fixes, dans lequel le moyen de circuit (31,32) fournit une série d'impulsions électriques bénignes à la première électrode en réponse auxdits états détectés et ladite seconde électrode est disposée pour coopérer avec ladite première électrode pour causer la libération iontophorétique de la substance médicinale dans la direction voulue pour fournir la médication au tissu d'intérêt proche.

2. Appareil selon la revendication 1, dans lequel ledit tissu d'intérêt est par exemple un site arythmogène de tissu cardiaque atteint d'un infarctus, lesdites électrodes (11,12) sont des électrodes de défibrillation en pièce et ledit médicament est un agent antiarythmique.

3. Appareil selon la revendication 1 ou 2, dans lequel ladite première électrode (11) comprend en outre une entrée (13) destinée à recevoir la médication provenant dudit moyen de stocka-

ge (23), une chambre de stockage (21) séparée dudit tissu par une membrane perméable (22) à travers laquelle ledit médicament peut être libéré et un orifice d'évacuation (16) par lequel le médicament inutilisé peut être sécrété.

4. Appareil selon l'une quelconque des revendications précédentes, dans lequel le moyen de stockage (23) est une poche implantable de façon sous-cutanée.

5. Appareil implantable selon l'une quelconque des revendications précédentes en conjonction avec un défibrillateur implantable, dans lequel ladite source (35) est une source d'électricité pour le défibrillateur implantable, le moyen de circuit (31,32) étant reliés à ladite source (35) pour fournir des impulsions de courant de défibrillation auxdites électrodes (11,12) ; les moyens de détection d'états (25,26) étant aptes à fonctionner pour détecter des états médicaux dans ledit tissu d'intérêt nécessitant une défibrillation ; et ledit moyen de commande (36) étant apte à fonctionner pour activer et désactiver lesdites impulsions de défibrillation en réponse aux états détectés ou à des intervalles fixes.

Fig. - 1

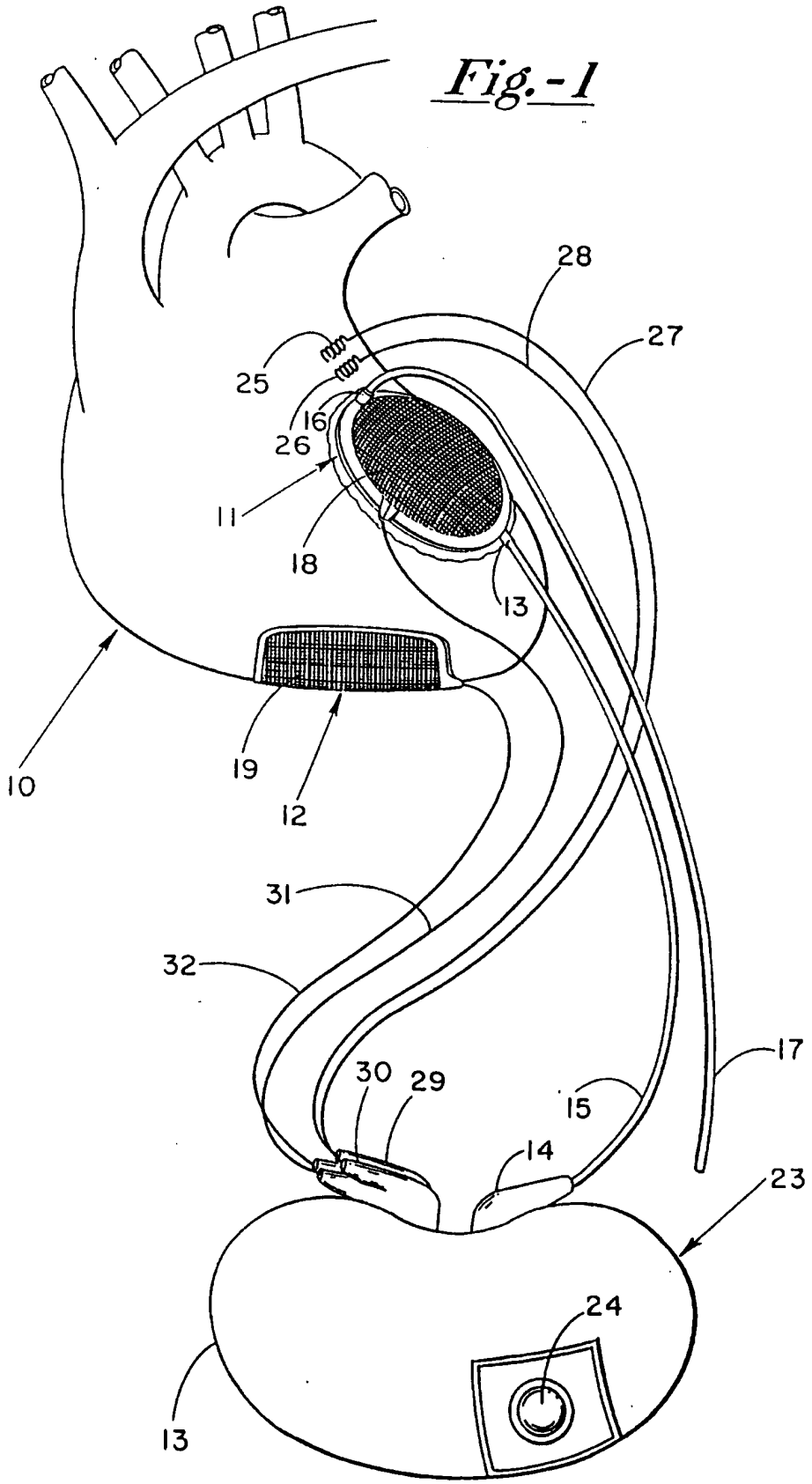


Fig.-2

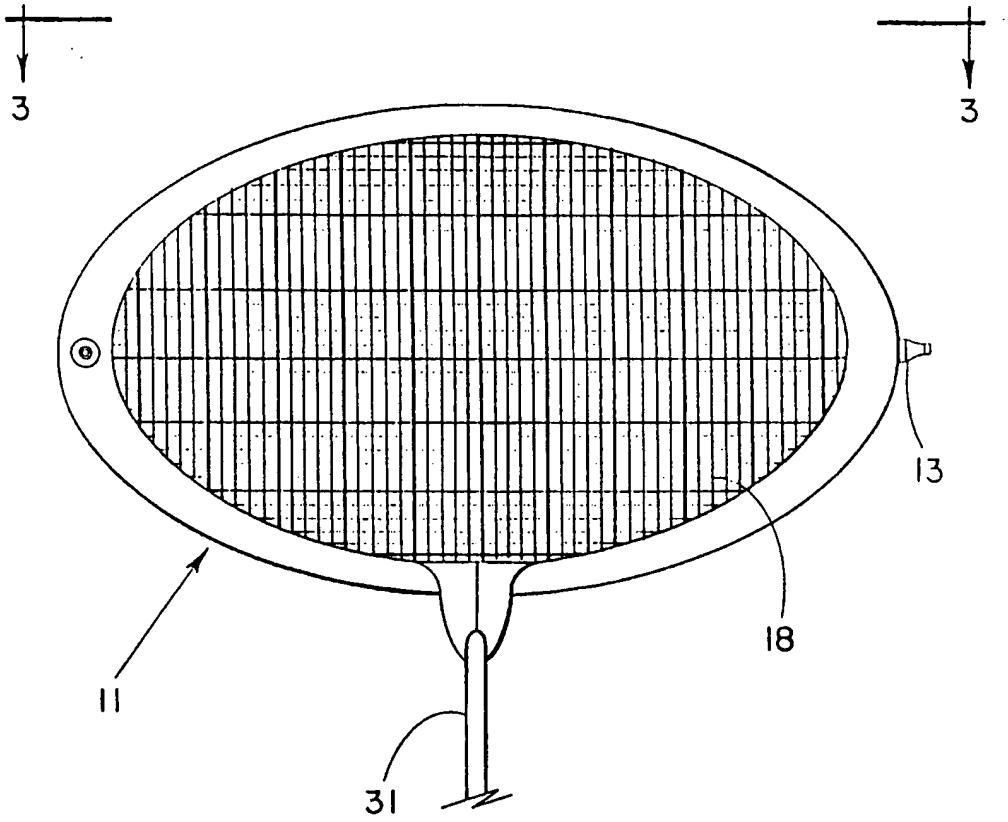


Fig.-3

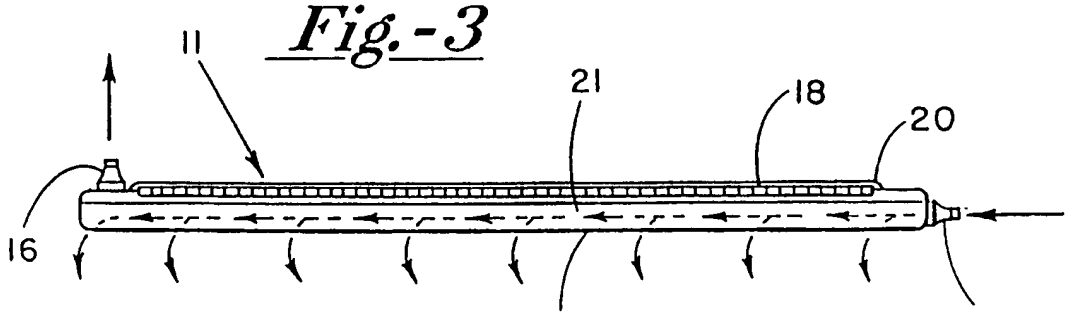
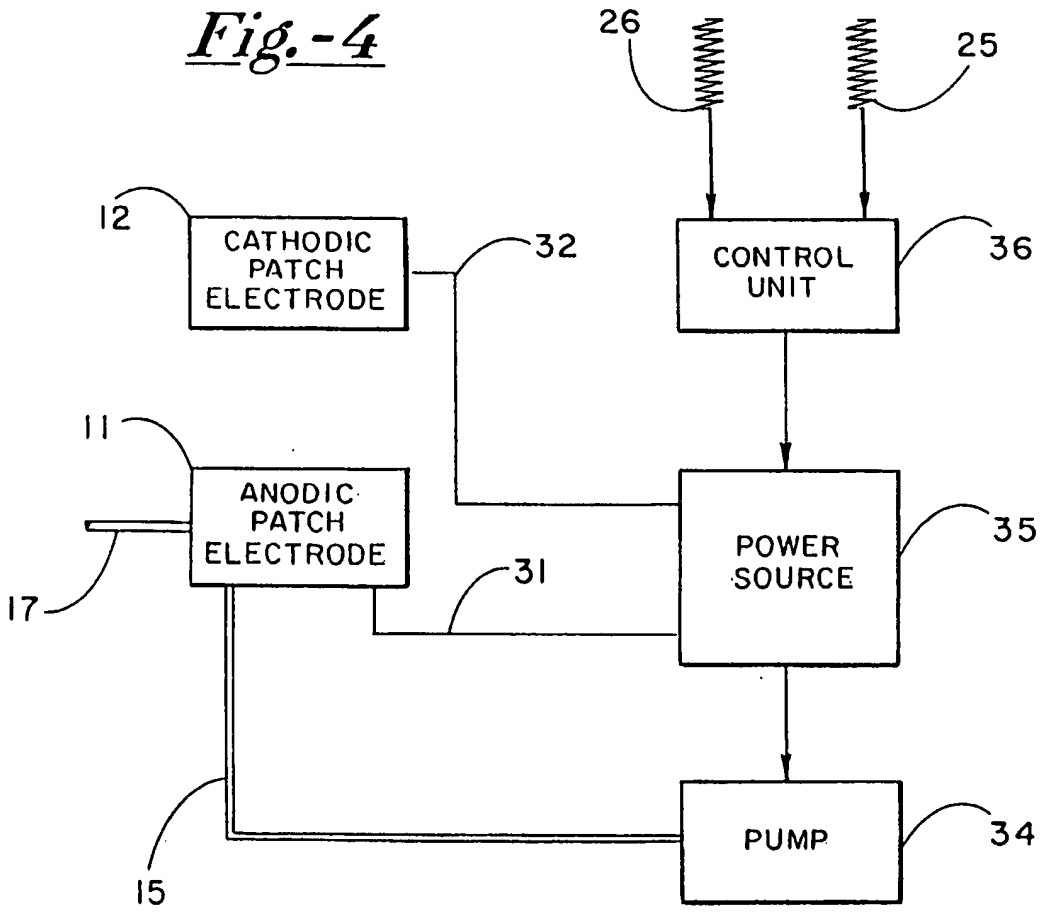


Fig.-4


26
25
12
CATHODIC PATCH ELECTRODE
32
CONTROL UNIT
36
11
ANODIC PATCH ELECTRODE
17
31
POWER SOURCE
35
PUMP
34
15